# Treatment and outcome of patients suffering from perineal/perianal rhabdomyosarcoma: results from the cws trials-retrospective clinical study

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Abstract: OBJECTIVES: To analyze the clinical course, treatment, complications, outcome, and quality of life (QOL) in patients with perineal/perianal rhabdomyosarcoma (PRMS) treated within the CWS-86, -91, -96, and -2002P trials. BACKGROUND:: Although multiple international study trials exist for the treatment of rhabdomyosarcoma, only very limited information is given on treatment, outcome, and QOL in PRMS. METHODS:: A total of 35 patients suffering from PRMS were treated with neoadjuvant chemotherapy. Local therapy with radiation and/or surgery was performed, followed by adjuvant chemotherapy. Functional long-term follow-up was evaluated by a gastrointestinal/QOL survey. RESULTS: Thirty-two patients were evaluated (exclusion n = 3). Eight patients had embryonal histology, and 24 patients had alveolar histology. The median age was 108 months (median follow-up: 5.8 years). The 5-year overall survival was 47% (95% confidence interval: 29-64). Sixteen IRS (Intergroup Rhabdomyosarcoma Study) III and IV patients had locoregional lymph node involvement at diagnosis. Seven patients were treated with chemotherapy/surgery alone [5-year event-free survival (EFS): 85.7%]. Eleven patients received only radiochemotherapy (5-year EFS: 27.3%). Combined radiochemotherapy/surgery was used in 12 patients (5-year EFS: 63.6%). Two patients were treated only with chemotherapy and they died. Patients with embryonal histology had a significantly better 5-year EFS (87.5%) than patients with alveolar histology (39.1%; P = 0.013). Some patients reported symptoms of fecal incontinence. The median Wexner fecal incontinence score was 9 (possible range: 0-20), and the median QOL score was 90.5 (applicable range: 0-144). CONCLUSIONS:: The outcome of these patients remains unsatisfactory. Prognostic factors for a favorable outcome are tumor size of smaller than 5 cm, negative locoregional lymph nodes, age less than 10 years, low IRS group, and embryonal histology. Fecal incontinence seems to be a problem.

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# Treatment and Outcome of Patients Suffering From Perineal/Perianal Rhabdomyosarcoma

## *Results From the CWS Trials—Retrospective Clinical Study*

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**Objectives:** To analyze the clinical course, treatment, complications, outcome, and quality of life (QOL) in patients with perineal/perianal rhabdomyosarcoma (PRMS) treated within the CWS-86, -91, -96, and -2002P trials.

**Background:** Although multiple international study trials exist for the treatment of rhabdomyosarcoma, only very limited information is given on treatment, outcome, and QOL in PRMS.

**Methods:** A total of 35 patients suffering from PRMS were treated with neoadjuvant chemotherapy. Local therapy with radiation and/or surgery was performed, followed by adjuvant chemotherapy. Functional long-term follow-up was evaluated by a gastrointestinal/QOL survey.

**Results:** Thirty-two patients were evaluated (exclusion n = 3). Eight patients had embryonal histology, and 24 patients had alveolar histology. The median age was 108 months (median follow-up: 5.8 years). The 5-year overall survival was 47% (95% confidence interval: 29–64). Sixteen IRS (Intergroup Rhabdomyosarcoma Study) III and IV patients had locoregional lymph node involvement at diagnosis. Seven patients were treated with chemotherapy/surgery alone [5-year event-free survival (EFS): 85.7%]. Eleven patients received only radiochemotherapy (5-year EFS: 27.3%). Combined radiochemotherapy/surgery was used in 12 patients (5-year EFS: 63.6%). Two patients were treated only with chemotherapy and they died. Patients with embryonal histology had a significantly better 5-year EFS (87.5%) than patients with alveolar histology (39.1%; $P = 0.013$). Some patients reported symptoms of fecal incontinence. The median Wexner fecal incontinence score was 9 (possible range: 0–20), and the median QOL score was 90.5 (applicable range: 0–144).

**Conclusions:** The outcome of these patients remains unsatisfactory. Prognostic factors for a favorable outcome are tumor size of smaller than 5 cm, negative locoregional lymph nodes, age less than 10 years, low IRS group, and embryonal histology. Fecal incontinence seems to be a problem.

**Keywords:** anus, outcome, perineum, quality of life, rhabdomyosarcoma

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Rhabdomyosarcomas of the perineum and the perianal region [or perineal/perianal rhabdomyosarcoma (PRMS)] are extremely rare and occur in less than 2% of all primary cases.[1] The 2 main histological subtypes are embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma. Alveolar histology is found more frequently in PRMS than those at other locations.[2] In addition, patients often have regional lymph node involvement and, at times, distant metastases.[2] Tumors are sometimes misdiagnosed as perirectal or gluteal abscess, delaying early diagnosis and appropriate therapy.[3] The prognosis of patients with PRMS is relatively poor. Patients treated within IRS I–IV trials had a 5-year overall survival (OS) rate of only 49%.[4,5] Positive predictive factors described for a favorable outcome are tumor size of smaller than 5 cm, less advanced clinical group and stage, negative regional lymph node status, and age less than 10 years.[5] Surprisingly, histology has not been described to significantly affect the outcome.[5] To date, there exist no data regarding stool continence and quality of life (QOL) in children with PRMS after treatment. The aim of this study was to analyze patients treated within the Cooperative Soft Tissue Sarcoma trials CWS-86, -91, -96, and -2002P of the Society of Pediatric Hematology and Oncology (GPOH) regarding treatment efficacy, including complications, outcome, positive predictive factors, incontinence, and QOL.

## PATIENTS AND METHODS

### Patients

More than 3500 patients with centrally reviewed (IL) histological diagnosis of rhabdomyosarcoma were treated in 32 participating institutions in Germany and Switzerland and were enrolled on the Cooperative Soft Tissue Sarcoma Studies CWS-86, -91, -96, and -2002P of the Society of Pediatric Oncology and Hematology (GPOH) between 1986 and 2008. Thirty-five patients with a diagnosis of PRMS were identified. Three patients were excluded because of an incomplete data set (n = 2) or age more than 21 years at initial diagnosis (n = 1). The appropriate ethical committee approved the trials. The patients, guardians or parents, or both gave written informed consent for participation on the trials.

### Study Design

#### *Risk Stratification for Systemic Treatment*

All patients received multiagent chemotherapy with at least 3 drugs, including alkylators, dactinomycin, and vincristine, depending on risk stratification and trial. Patients treated within the CWS-86 trial underwent chemotherapy with VAIA (vincristine, ifosfamide, doxorubicin, dactinomycin).[6] In the CWS-91 trial, chemotherapy was carried out according to the VACA (vincristine, dactinomycin, doxorubicin, cyclophosphamide) for standard risk group patients or EVAIA regimen (etoposide, vincristine, dactinomycin, ifosfamide, doxorubicin) for high-risk patients (all patients with IRS group III except orbital and non–bladder-prostata genitourinary localization).[7]

In the CWS-96 trial, patients received IVA (ifosfamide, vincristine, dactinomycin) in the standard risk group. In the high-risk group, patients were randomized to VAIA (vincristine, ifosfamide, doxorubicin, dactinomycin) or CEVAIE (carboplatin, epirubicin, vincristine, dactinomycin, ifosfamide, etoposide).[8] In the CWS-2002P trial, standard risk group patients were treated with $I^2VA$ (ifosfamide, vincristine, dactinomycin). In the high-risk group, this therapy was broadened by doxorubicin.

Neoadjuvant chemotherapy was prescribed for the majority of patients with macroscopic residual tumors after initial biopsy (IRS group III). In this group, radiographical response was assessed after 9 weeks using computed tomography (CT) or magnetic resonance imaging (MRI), as further (local and systemic) treatment was response dependent.

### *Radiotherapy*

The treatment protocol included radiotherapy in children older than 1 year. Children younger than 3 years should be treated with a radiation dosage of 32 Gy. Protection of the pelvic/hip growth plates was recommended to avoid growth disturbances. The target volume was based on the initial tumor volume on MRI plus a 2-cm margin. The radiation dose was stratified on response to chemotherapy, IRS group, and histology. Patients with complete response or good response (definition of response is described later) at radiological response assessment and favorable (embryonal) histology should undergo hyperfractionated, accelerated radiotherapy (HART) of 32 Gy to the primary site (1.6 Gy twice daily). Patients with poor response received a total of 44.8 Gy HART. Patients who did not qualify for HART (eg, necessity of repeated anesthesia at young age or gut/liver involvement) received conventional fractionation with 1.8 Gy per day (overall dose: 39.8 or 50 Gy). Lower dose was used for irradiation of the abdomen or if a dose reduction was necessary (age or tumor localization). For a better comparison between the groups, patients were assigned to a group ($\leq$36 Gy and $>$36 Gy).

### *Surgery*

Surgical guidelines did not recommend a primary tumor resection unless a primary complete tumor resection without microscopic residual disease seemed to be feasible. In all other cases, a primary biopsy (open or tru-cut) should be carried out to establish a histological diagnosis. Secondary surgery after chemotherapy and/or radiotherapy was carried out if a residual tumor mass was detected at the time of response assessment. Mutilating surgery (resection of the rectum, exenteration of the pelvis) was allowed after neoadjuvant therapy. The extent of tumor resection was defined in the following way: R0 = complete tumor resection without microscopic residual disease; R1 = tumor resection with microscopic residual disease; and R2 = tumor resection with macroscopic residual disease.

### *Definition of Treatment Groups and Response to Preoperative Chemotherapy*

Patients were evaluated regarding local treatment. Therefore, patients were assigned to 4 different local treatment groups. In group 1, patients were treated with chemotherapy and surgery alone. In group 2, patients were treated with chemotherapy and radiotherapy. In group 3, patients were treated with chemotherapy, radiotherapy, and tumor resection (radiotherapy plus surgery). In group 4, patients received only chemotherapy. Patients were additionally subgrouped according to tumor size ($\leq$5 or $>$5 cm), patients' age ($<$10 or $\geq$10 years), locoregional lymph node status (negative or positive), and the IRS group.

Complete response was assumed if there was a lack of visible tumor on CT/MRI or no evidence for viable tumor during second-look surgery. Good response was defined as a tumor volume reduction of more than two-thirds. Poor response was a tumor volume reduction between one-third and two-thirds. Objective response was presumed if the reduction was less than one-third and more than the baseline. Progressive disease described any tumor progression.

### *Assessment of Postoperative Bowel and Bladder Function*

To assess the postoperative bowel and bladder function of the treated patients and for the acquisition of possible radiotherapy-related restrictions of the pelvic mobility, a questionnaire was sent to surviving patients by mail. The questionnaire inquired about the quality, quantity, frequency, and problems of bowel movements. Second, subjective stool incontinence and symptoms of constipation were analyzed. In addition, the voiding behavior and problems with walking were evaluated. Fecal incontinence was also graded using the Wexner fecal incontinence score, with a possible range from 0 to 20.[9]

### *QOL Assessment*

QOL assessment was carried out using an established gastrointestinal QOL questionnaire, which was initially described by Eypasch and colleagues.[10] This validated questionnaire assesses 36 items concerning physical, functional, mental, and social status. For each question, there are 5 possible answers, assigned a numeric value from 0 (lowest score) to 4 (highest score).[10,11] The maximum score is 144 and the lowest score is 0. A high score correlates with a high QOL. The QOL questionnaire was also sent by mail to all surviving patients.

### Statistical Analysis

The 5-year OS and the 5-year event-free survival (EFS) were calculated by Kaplan-Meier estimates. For the OS, the time from primary diagnosis to death (therapy related or other reasons) or last follow-up (censored observations) was used. For the EFS, the endpoint was defined as the time from diagnosis to first relapse. Kaplan-Meier estimates are given with log–log-transformed 95% confidence intervals (CIs).[12] The Mantel-Cox log rank test was used to test the difference between survival curves. Cox proportional hazards analysis was performed to calculate single variable and adjusted risk ratios, with 95% CIs for risk factors. Demographic data are reported as median (interquartile range). A $P$ value less than 0.05 was considered significant. The statistical analyses were performed using the IBM SPSS 20 software.

## RESULTS

### Patients

The characteristics of the 32 evaluated patients are shown in Table 1. Response evaluation in IRS group III was not possible for 1 patient, in whom the tumor volume was not measured, as the suggested imaging was not carried out at the correct time point. In IRS group IV, response could not be assessed for 2 patients for the same reasons. The 5-year EFS for different IRS groups are shown in Figure 1.

### Radiotherapy

Twenty-three of 32 patients underwent radiotherapy. The different local treatment groups are shown in Table 2. Patients underwent either radiotherapy alone or radiotherapy followed by tumor resection. An incomplete tumor resection without preoperative radiotherapy was not recommended by the study protocols. Radiation doses ranged from 32 to 64 Gy. Doses 36 Gy or less were used for 7 patients (HART: 5; conventional fractionation: 1; brachytherapy: 1). Doses more than 36 Gy were used for 16 patients (HART: 13; conventional: 3). There was no significant difference regarding the

 

**TABLE 1.** Patients' Data

| | |
|---|---|
| Patients' age, median [interquartile range] | 108 mo [3–204] |
| <10 yr | n = 15 (RME: n = 6; RMA: n = 9) |
| ≥10 yr | n = 17 (RME: n = 2; RMA: n = 15) |
| Sex distribution | Male: 16; female: 16 |
| Histological subtype | RME: n = 8<br>RMA: n = 24 |
| IRS group | I: n = 2 (RMA: n = 1; RME: n = 1)<br>II: n = 4 (RMA: n = 2; RME: n = 2)<br>III: n = 18 (RMA: n = 13; RME: n = 5)<br>IV: n = 8 (RMA: n = 8; RME: n = 0) |
| Primary tumor localization | Perianal: n = 24<br>Perineal: n = 8 |
| Suspected lymph node involvement at initial diagnosis | N0: n = 16 (RME: n = 6; RMA: n = 10)<br>N1: n = 16 (RME: n = 2; RMA: n = 14; IRS III: n = 9; IRS IV: n = 7) |
| Tumor size | ≤5 cm: n = 11 (RMA: n = 7; RME n = 4)<br>>5–10 cm: n = 16 (RMA: n = 13; RME n = 3)<br>>10 cm: n = 5 (RMA: n = 5; RME: n = 0) |
| Response in IRS group III patients (n = 18) | CR: n = 4<br>GR: n = 9<br>PR: n = 4<br>Not assessable: n = 1 |
| Response in IRS group IV patients (n = 8) | CR: n = 1<br>GR: n = 3<br>PR: n = 2<br>Not assessable: n = 2 |
| Follow-up, median [interquartile range] | Whole group: 47 mo [11–394]<br>Patients alive: 91 mo [17–394] |

Patients' data and response of evaluable IRS group III and IV patients to induction chemotherapy.

CR indicates complete response; GR, good response; PR, poor response; RMA, alveolar rhabdomyosarcoma; RME, embryonal rhabdomyosarcoma.

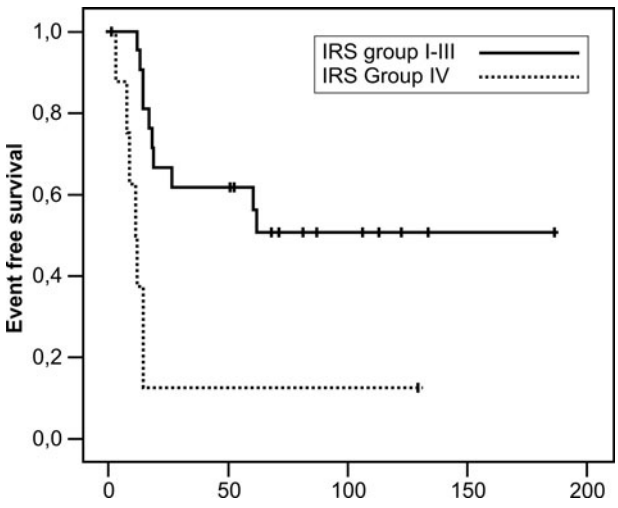


**FIGURE 1.** Kaplan-Meier estimation presenting EFS in IRS group I–III compared with IRS group IV ($P < 0.05$).

5-year EFS rate between patients who were irradiated with a dose of 36 Gy or less (33.3%) compared with patients who underwent radiotherapy with a dose of more than 36 Gy (52.2%; $P = 0.62$), given that the irradiation dose was risk adapted (Fig. 2). Eight of 11 patients treated only with radiotherapy had locoregional lymph node involvement, and 4 of 11 patients were in IRS group IV. Early complications of radiotherapy, including dermatitis, leucopenia, epidermiolysis, diarrhea, proctitis, and cystitis, were reported in 57% of the patients (13/23). Late effects of radiotherapy, including growth retardation of the pelvis, urinary incontinence, low compliance of the bladder, and stricture of the urethra, were observed in 3 patients.

## Surgery

### *Primary Surgery*

Twenty-four patients underwent initial tumor biopsy (open biopsy: n = 20; needle biopsy: n = 2; perineal punch biopsy: n = 1; MRI-guided biopsy: n = 1). Regional lymph node sampling was done in 8 of these patients, all of which showed tumor-positive results. Eight patients were treated with primary tumor resection (resection status R0: n = 2; R1: n = 5; R2: n = 1). Regional lymph node sampling was carried out in 1 patient undergoing primary tumor resection without detection of tumor cells. Minor surgical complications (wound healing disorders) occurred in 3 patients after biopsy and in 1 patient after tumor resection. There was no difference with respect to primary biopsy or tumor resection regarding complications.

### *Secondary Surgery*

One patient underwent secondary tumor biopsy, in which no tumor cells could be detected. Twelve patients were treated with secondary tumor resection (resection status R0: n = 2; R1: n = 3; R2: n = 4; not assessable: n = 3). Additional regional lymph node sampling was carried out for 3 patients, of which 1 showed tumor-negative findings and 2 were not assessable after chemotherapy. Minor surgical complications occurred in 2 patients, who developed wound-healing disorders. The complete overview and outcome of different treatment groups are shown in Table 2.

## Positive Predictive Factors for Outcome

On the basis of the predescribed positive predictive factors of Blakely and colleagues,[5] we investigated whether these positive predictive factors could also be identified in our cohort. Positive predictive factors for outcome in our group were patients' age of less than 10 years, tumor size 5 cm or smaller, negative locoregional lymph node involvement, low IRS group, and embryonal histology (Tables 3, 4).

## Overall Survival

The 5-year OS and EFS rate for the whole group was 47% (95% CI: 29–64).

## Assessment of Postoperative Bowel and Bladder Function

The questionnaires were answered and sent back by only 5 of 15 surviving patients despite forwarding 2 additional reminders to the participating centers. The oldest patient alive is currently 34 years of age, so many of the patients may have left the pediatric aftercare. All patients answering the questionnaire underwent radiotherapy. For 4 patients, radiotherapy was combined with surgical tumor resection. All patients reported neither voiding problems nor limitations in pelvic motility as an indicator for impairments after radiotherapy. Three of 5 patients reported defecation problems and symptoms of fecal incontinence while having pasty stools. Four patients were able to discriminate between air, pasty, and solid stool. Three patients had a

**TABLE 2.** Five-year EFS Results in Different Treatment Groups

| Treatment Group | IRS Group | Time Point of Surgery | Histology | No. Patients | Resection Status at Primary or Secondary Surgery, n | EFS, % [95% CI] |
|---|---|---|---|---|---|---|
| Chemotherapy and surgery alone (Surgery) | All | | | **7** | | **85.7 [33.4–97.9]** |
| | I–III | | | 7 | | 85.7 |
| | IV | | | 0 | | |
| | | | RMA | 4 | R0: 2<br>R1: 2<br>R2: 0 | 75.0 |
| | | | RME | 3 | R0: 1<br>R1: 1<br>R2: 1 | 100 |
| | | Primary | | 5 | R0: 2<br>R1: 3<br>R2: 0 | 60 |
| | | Secondary | | 2 | R0: 1<br>R1: 0<br>R2: 1 | 100 |
| Radiochemotherapy with combined tumor resection (RT + Surgery) | All | | | **12** | | **63.6 [29.7–84.5]** |
| | I–III | | | 10 | | 66.7 |
| | IV | | | 2 | | 50.0 |
| | | | RME | 2 | R0: 0<br>R1: 1<br>R2: 1 | 100 |
| | | | RMA | 10 | R0: 1<br>R1: 3<br>R2: 3<br>Not assessable: 3 | 55.6 |
| | | Primary (before RT) | | 2 | R0: 0<br>R1: 1<br>R2: 1 | 100 |
| | | Secondary (after RT) | | 10 | R0: 1<br>R1: 3<br>R2: 3<br>Not assessable: 3 | 60 |
| Solely chemotherapy (CT) | IV | | | **2** | | **0** |
| | | | RME | 0 | | |
| | | | RMA | 2 | | 0 |
| Solely radiochemotherapy (RT) | All | | | **11** | | **27.3 [6.5–53.9]** |
| | I–III | | | 7 | | 42.9 |
| | IV | | | 4 | | 0 |
| | | | RME | 3 | | 66.7 |
| | | | RMA | 8 | | 12.5 |

Five-year EFS in different treatment groups. Bold numbers are the total number per group. There was a statistical significant difference between the following groups: Surgery vs CT: $P = 0.002$; RT + Surgery vs CT: $P = 0.035$; RT vs Surgery: $P = 0.014$; RT vs RT + Surgery: $P = 0.044$, but treatment allocation was not randomized and treatment groups are not clinically equivalent.

RMA indicates alveolar rhabdomyosarcoma; RME, embryonal rhabdomyosarcoma.

stool frequency of more than 2 and fewer than 6 per day. Two patients had a stool frequency of only 1 to 2 per day. Two patients constantly had to wear diapers. The median Wexner fecal incontinence score was 9 (min: 6; max: 16) (0 = no stool incontinence; 20 = complete stool incontinence).

## QOL Assessment

Four of 5 patients responding to the QOL questionnaire completed the questionnaire entirely. The median QOL score was 90.5 (min: 74; max: 106) [lowest possible score 0 (no QOL), highest score 144 (good QOL)].

## DISCUSSION

PRMS is rare and only a very limited number of patients have been described.[2,5,13] The largest published series by Blakely and colleagues[5] described several risk factors for a favorable outcome, including a primary tumor size of smaller than 5 cm, less advanced clinical group and stage, negative regional lymph node status, and age less than 10 years. The histological subtype did not significantly

affect the outcome in their trial.[5] In PRMS, alveolar histology is more often found than those in other locations and has been shown to be accompanied by a less favorable prognosis.[2] In IRS I–IV, 65% of the patients had alveolar or undifferentiated histology.[5] In our study, 75% of the patients had alveolar histology. In contrast to the IRS results, the histological subtype significantly affected the outcome of our patients. The 5-year EFS rate was 39.1% in patients with alveolar histology compared with 87.5% in patients with embryonal tumors ($P = 0.013$). The detailed analysis of our smaller study cohort showed some well-defined differences in comparison with the IRS I–IV trials. In our series, patients with embryonal histology had less regional lymph node involvement, were mostly younger than 10 years, had no metastases, were often in lower IRS groups, and had only 2 local relapses. In contrast, patients with alveolar histology often had locoregional lymph node involvement, were mostly older than 10 years, had more distant metastases, were mostly in higher IRS groups, and had an increased number of local relapses. Therefore, these factors may account for the significant difference between the 2 histological subgroups.

Another risk factor was the primary tumor size. Most of our patients had a tumor size of larger than 5 cm and had a higher clinical stage. This observation was also made by Blakely and colleagues.[5] The reason might be that older children tend to hide their intimate areas from their parents and therefore lesions are diagnosed later. The outcome of children with a tumor size of smaller than 5 cm was much better (5-year EFS rate: 81.8%) than those with a tumor size of larger than 5 cm (35%; $P = 0.027$).

In IRS I–IV trials, 64% of the patients presented with advanced stage tumors (IRS III/IV).[5] In our study, 81% of the patients had advanced stage disease. We found a statistically significant difference between IRS group I–III patients and IRS group IV patients. Therefore, metastatic disease is a negative prognostic factor in our series.

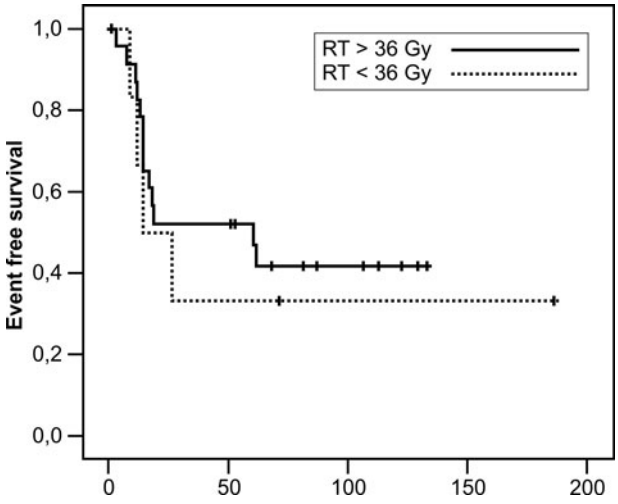


**FIGURE 2.** Kaplan-Meier estimation for EFS for treatment with different radiotherapy doses ($P = 0.62$).

**TABLE 3.** Positive Predictive Factors on Outcome

| Risk Factor | No. Patients | EFS, % [95% CI] | *P* |
|---|---|---|---|
| Tumor size | | | |
| ≤5 cm | 11 | 81.8 [44.7–95.1] | 0.027 |
| >5 cm | 21 | 35 [15.7–55.2] | |
| Age | | | |
| <10 yr | 15 | 78.6 [47.2–92.5] | 0.004 |
| ≥10 yr | 17 | 29.4 [10.7–51.1] | |
| Locoregional lymph node involvement | | | |
| + | 16 | 26.7 [8.3–49.6] | 0.002 |
| − | 16 | 75 [46.3–89.8] | |
| Histology | | | |
| RME | 8 | 87.5 [38.7–98.1] | 0.013 |
| RMA | 24 | 39.1 [19.9–58.0] | |
| IRS group | | | |
| I–III | 24 | 65.2 [42.3–80.8] | <0.001 (Fig. 1) |
| IV | 8 | 12.5 [0.7–42.3] | |

RMA indicates alveolar rhabdomyosarcoma; RME, embryonal rhabdomyosarcoma.

**TABLE 4.** Cox Regression Analysis for Risk Factors

| Risk Factor | Patients With Events | Risk Ratio [95% CI] | *P* | Adjusted Risk Ratio* |
|---|---|---|---|---|
| Tumor size | | | | |
| ≤5 cm | 3/11 | 3.76 | 0.021 | 2.32 |
| >5 cm | 14/21 | [1.19–16.6] | | 2.73 |
| Age | | | | |
| <10 yr | 4/15 | 4.57 | 0.040 | 2.14 |
| ≥10 yr | 13/17 | [1.59–16.4] | | |
| Lymph node involvement | | | | |
| + | 12/16 | 4.45 | 0.003 | |
| − | 5/16 | [1.62–14.2] | | |
| Histology | | | | |
| RME | 1/8 | 8.36 | 0.005 | |
| RMA | 16/24 | [1.7–151.1] | | |
| IRS group | | | | |
| I–III | 10/24 | 5.27 | 0.003 | |
| IV | 7/8 | [1.85–14.3] | | |

*Adjusted for tumor size, lymph node involvement, and IRS group.
Single variable and multifactorial Cox regression analysis showing the effect of selected factors on the risk of events.
RMA indicates alveolar rhabdomyosarcoma; RME, embryonal rhabdomyosarcoma.

Locoregional lymph node involvement is often found in patients with PRMS and is reported to be highest among all sites in rhabdomyosarcoma.[2,14] In the complete IRS I–IV trials, 46% of the patients had proven locoregional lymph node involvement.[5] In our series, 50% of the patients had positive lymph nodes and they had a statistically significant worse outcome. Seven of 16 patients were in IRS group IV. Therefore, the evaluation of locoregional lymph nodes needs to be continued in future CWS trials. Blakely and colleagues reported that positive lymph nodes are underestimated by CT and suggested surgical evaluation of regional lymph nodes.[5] In the CWS trials, MRI scans were used for the evaluation of lymph nodes, which offered a better soft-tissue contrast. Positron emission tomography (PET) and PET/CT seem to be even more beneficial in the diagnosis of lymph node lesions in rhabdomyosarcoma,[15,16] but the final role of PET/CT in rhabdomyosarcoma is unclear. This should be taken into account during diagnostic workup, as further intensified therapy including radiotherapy might be required for the management of these lymph nodes.[5]

Another important point is the age of the patients. Patients younger than 10 years have a better outcome than older patients,[5] which could also be confirmed in our series. This might be caused by the fact that patients younger than 10 years more often present with embryonal rhabdomyosarcoma than older patients. In addition, 15 of 17 patients 10 years or older had a tumor size of larger than 5 cm. A possible explanation might be that tumors in young children are diagnosed earlier because they are more often inspected by their parents.

Taken together, we could confirm Blakely and colleagues' positive predictive factors for survival, including primary tumor size of smaller than 5 cm, low clinical group/no IRS group IV disease, negative locoregional lymph node involvement, and age less than 10 years. In addition, we found that embryonal histology is a prognostic factor for survival.

The optimal treatment modality for patients with PRMS is unclear. Within the CWS trials, patients were stratified for local control on the basis of several criteria such as assessment of resectability and tumor size and location. The principle of the CWS trials was that all patients should receive radiotherapy before surgery except if there was a contraindication for radiotherapy (eg, age $<1$ year, field) or if a nonmutilating R0 resection was feasible. Patients received treatment in 4 groups. The best outcome regarding the 5-year EFS was found among the 7 patients undergoing surgical tumor resection and chemotherapy (85.7%). These results are better than among patients treated with radiochemotherapy and tumor resection (5-year EFS: 63.6%), but it must be taken into account that 3 of 7 patients had embryonal rhabdomyosarcoma and that only 1 of 7 patients had locoregional lymph node involvement, resulting in a better outcome. The question whether primary or secondary surgery is more beneficial for the outcome cannot be answered because of the small size of the cohort. Only 3 of 7 patients had a microscopically complete tumor resection, yet only one patient had a local relapse. Interestingly, these patients underwent primary microscopic complete tumor resection. Most of the patients treated with combined radiochemotherapy and tumor resections had alveolar histology and were the more challenging tumors for local control. Five of 12 patients had locoregional lymph node involvement. A microscopic complete tumor resection was achieved in only one patient. Four patients in this group had a local relapse, of which only one patient underwent R0 resection. The necessity of a complete tumor resection in this location after radiochemotherapy remains unclear. Although reexcisions of primary lesions after primary surgery are recommended to achieve clinical group I,[5] the indication for microscopic complete mutilating secondary surgery remains—based on our data—unclear. Patients treated with radiochemotherapy alone had a significantly worse outcome compared with patients treated with chemotherapy and surgery or with radiochemotherapy and surgery, taking into account that 8 of 11 patients had locoregional lymph node involvement and 4 of 11 patients had local relapse. Therefore, radiation therapy was used for patients with tumors, which were judged as inoperable, and obviously the outcome was worse in these patients. The use of risk-adapted radiation therapy doses seemed to be reasonable in our cohort, but one must interpret these findings cautiously because an evaluation of different radiation dose levels in the single-risk groups has not been possible. An analysis of larger numbers will be required to finally answer this question. Chemotherapy alone is not an alternative for these patients; in our studies, it was used for rapidly progressing patients who could not undergo local control.

The assessment of postoperative bowel and bladder function was limited in our series. The reason for the low survey response rate remains unclear, but it might be due to the long period of observation and the challenges in locating patients. Nevertheless, 3 of 5 patients had fecal incontinence, which correlated with an increased Wexner fecal incontinence score. Therefore, improvements of local control including evaluation of proton beam therapy and brachytherapy might be studied in future CWS trials regarding treatment efficacy and side effects. QOL assessment revealed a low median QOL score of 90.5 in comparison with patients undergoing surgery for other colorectal tumors. Patients undergoing sigmoid colectomy for carcinomas had a median QOL score of 106 of 113 depending on the surgical approach performed.[11] In our series, fecal incontinence seems to be the most serious problem for the patients, resulting in a lower QOL score.

## CONCLUSIONS

Patients with PRMS are a high-risk population with a higher proportion of alveolar histology and locoregional lymph node involvement than at other sites. Surgical evaluation of lymph nodes, followed by appropriate therapy, was carried out in the CWS trials in the past and was found to be appropriate. Novel diagnostic imaging tools such as PET/CT or PET/MRI may be useful for evaluation of suspicious lymph nodes and might replace the need for surgical evaluation but has yet to be defined. Several predictive risk factors for a more favorable prognosis could be identified. Besides systemic control by chemotherapy, local control should consist of surgical tumor resection or a combination of radiotherapy and surgery. Radiotherapy as the sole local therapy seems not to be adequate. In addition to oncological issues, fecal incontinence and QOL seem to be a problem of these patients and should be taken into account during treatment planning. Our preliminary QOL results underline that possible late effects should be taken into account in future treatment concepts.

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